2014

Sodium ion interactions with aqueous glucose: Insights from quantum mechanics, molecular dynamics, and experiment

Heather B. Mayes
Northwestern University

Jianhui Tian
Los Alamos National Laboratory

Michael W. Nolte
Iowa State University, mnolte@iastate.edu

See next page for additional authors

THE JOURNAL OF PHYSICAL CHEMISTRY B

Article

pubs.acs.org/JPCB

Sodium Ion Interactions with Aqueous Glucose: Insights from Quantum Mechanics, Molecular Dynamics, and Experiment

Heather B. Mayes,[†] Jianhui Tian,[‡] Michael W. Nolte,[§] Brent H. Shanks,[§,∥] Gregg T. Beckham,[⊥] S. Gnanakaran,*[,‡] and Linda J. Broadbelt*[,†]

[†]Department of Chemical and Biological Engineering, Northwestern University, Evanston, Illinois 60208, United States

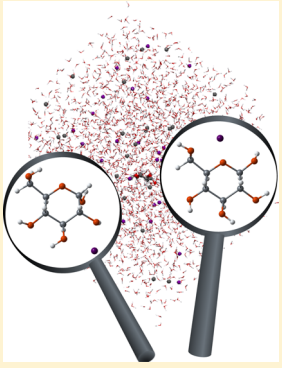
[‡]Theoretical Biology and Biophysics Group, Los Alamos National Laboratory, Los Alamos, New Mexico 87545, United States

[§]Department of Chemical and Biological Engineering, and [∥]Center for Biorenewable Chemicals (CBiRC), Iowa State University, Ames, Iowa 50011, United States

[⊥]National Bioenergy Center, National Renewable Energy Laboratory, Golden, Colorado 80202, United States

Supporting Information

ABSTRACT: In the last several decades, significant efforts have been conducted to understand the fundamental reactivity of glucose derived from plant biomass in various chemical environments for conversion to renewable fuels and chemicals. For reactions of glucose in water, it is known that inorganic salts naturally present in biomass alter the product distribution in various deconstruction processes. However, the molecular-level interactions of alkali metal ions and glucose are unknown. These interactions are of physiological interest as well, for example, as they relate to cation-glucose cotransport. Here, we employ quantum mechanics (QM) to understand the interaction of a prevalent alkali metal, sodium, with glucose from a structural and thermodynamic perspective. The effect on β-glucose is subtle: a sodium ion perturbs bond lengths and atomic partial charges less than rotating a hydroxymethyl group. In contrast, the presence of a sodium ion significantly perturbs the partial charges of α-glucose anomeric and ring oxygens. Molecular dynamics (MD) simulations provide dynamic sampling in explicit water, and both the QM and the MD results show that sodium ions associate at many positions with respect to glucose with reasonably equivalent propensity. This promiscuous binding nature of Na^+ suggests that computational studies of glucose reactions in the presence of inorganic salts need to ensure thorough sampling of the cation positions, in addition to sampling glucose rotamers. The effect of NaCl on the relative populations of the anomers is experimentally quantified with light polarimetry. These results support the computational findings that Na^+ interacts similarly with α- and β-glucose.



INTRODUCTION

Glucose, the monomer of the most abundant biomass component, cellulose,[1] has received attention as a renewable, alternative feedstock for fuels and chemicals.[2−6] One of the targets of these efforts is to improve the yield and selectivity of conversion of glucose to the platform chemical 5-hydroxymethylfurfural (HMF).[6] Several groups have investigated the use of inorganic salts for improving glucose conversion, either in the aqueous phase of a two-phase system[7,8] or in ionic liquid solvents.[9,10] While these inorganic salts have a significant impact on product partitioning in the reaction system, there are indications that they also can serve a catalytic role. A variety of salts have been tested, including NaCl, a naturally occurring component of biomass[11−13] and an inexpensive catalyst option that has been shown to increase HMF yield.[14−16] Combs and co-workers have proposed that the catalytic effect is due to glucose complexing with salts.[16] A better understanding of how inorganic salts interact with glucose in aqueous solution would provide a firm foundation for understanding and harnessing these observed effects of glucose−ion interactions. Additionally, Na^+−glucose interactions are physiologically important. The GLUT2 enzyme transports Na^+ and glucose in the liver, pancreas, intestine, kidney, and brain, and the Na^+-coupled glucose transporter (SGLT1) coshuttles water across membranes in functions such as intestinal sugar uptake.[17−19] A clearer picture of Na^+−glucose interactions could be of use in efforts toward a molecular understanding of how these enzymes function, which is a topic of current interest.[20]

Glucose conformations in the aqueous phase have been extensively studied, providing a baseline for the present study of aqueous glucose interactions with inorganic salt. NMR experiments have revealed the ratio of β- to α-glucose in aqueous solution to be approximately 2 to 1, with the ratio sensitive to temperature, and have demonstrated that the glucose molecules predominantly adopt the equatorial chair pyranose ring conformation ($^4C_1$).[21,22] NMR studies have also been employed to identify the conformation of the hydroxymethyl group on glucose. Its orientation can be identified as gauche−gauche (gg), gauche−trans (gt), or trans−gauche (tg) conformations based on the O5−C5−C6−

Received: September 23, 2013
Revised: December 3, 2013
Published: December 5, 2013

   dx.doi.org/10.1021/jp409481f | J. Phys. Chem. B 2014, 118, 1990−2000

O6 and C4−C5−C6−O6 dihedral angles, respectively, with this conventional identification of glucose atoms shown in Figure 1. Bock and Duus reviewed such efforts in the 1990s,

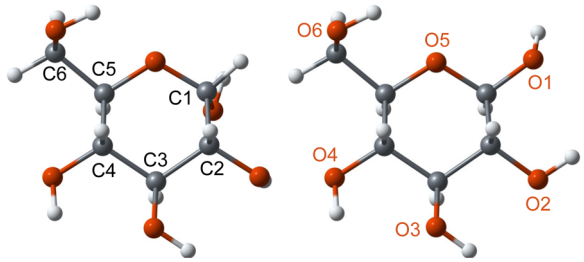


Figure 1. Low Gibbs free energy conformations of neat α-glucose showing conventional carbon numbering (left) and β-glucose showing conventional oxygen numbering (right).

noting approximate populations in glucose of 6:4:0 for gg:gt:tg.[23] Thibaudeau and co-workers used updated Karplus equations with their NMR experiments to conclude that gt is actually more abundant than gg, with tg less than 10% of the population for glucose.[24] Mason and co-workers followed up that study with combined MD and neutron diffraction with isotopic substitution experiments, arguing that gg dominates.[25] Despite differences in absolute numbers, the studies agree that gg and gt both contribute significantly to the equilibrium populations, with tg accounting for 10% or less of the population. A host of molecular dynamics (MD) studies of glucose in water reveal increasing agreement between experiment and theoretical models.[25−27] Quantum mechanical (QM) studies have also been completed, especially aimed at elucidating the anomeric effect.[28−30] Briefly, the anomeric effect refers to the stability of axial conformations of electronegative substituents at the C1 position in pyranose rings, contrary to what would be expected on the basis of only steric considerations.[31,32] The relative stability of the anomers is a function of the electrostatic environment; in vapor phase and nonpolar solvents, α-glucose is preferred, with the population shifting toward β-glucose as the polarity of the solvent increases.[31,33] As noted above, β-glucose is preferred in aqueous solution. Because the glucose−water interaction has been well-studied, with only a sampling of the relevant literature cited here, this work only reports properties of neat glucose to the extent that it allows us to contrast our results with inorganic salt using consistent methodology.

It has long been known that sugars and salts complex; in 1825, Calloud reported crystals of sugar and NaCl obtained from a diabetic individual's urine and from grapes,[34] which contain glucose as the primary sugar.[35,36] The 1960s and 1970s saw a renewed interest in interaction of carbohydrates and inorganic salts, exploring their behavior in aqueous solution, as reviewed by Angyal,[37,38] who performed significant work in this area. On the basis of paper ionophoresis studies with carbohydrates,[39] Angyal surmised that reducing sugars, such as glucose, complex specifically with the cation of the inorganic salt because they migrated toward the cathode.[38] Franks and co-workers also proposed that the cation has a greater effect on glucose than the anion based on differences in results seen by changing the cation while keeping the anion constant.[40] Rasrendra and co-workers came to the same conclusion based on finding little difference in results from studies with halide or sulfate salts.[14] Other notable conclusions from these studies include the hypothesis that a single carbohydrate hydroxyl interaction with cations cannot compete with solvent interactions; a combination of two or three hydroxyl groups with the cation is required.[38]

Franks and co-workers also noted that the addition of inorganic salts to aqueous glucose solutions can change the relative populations of glucose anomers.[40] Using Raman spectroscopy, they reported qualitative changes in the height of peaks associated with the different anomers, which correspond to an increased population of α-glucose when $CaCl_2$ was added to an aqueous glucose solution, with a more subtle perturbation found with NaCl. We are not aware of any experimental studies that quantify the populations of α- versus β-glucose in the presence of Na^+ or as a function of NaCl concentration. We are also not aware of experimental studies identifying the hydroxymethyl orientations of glucose with NaCl in the aqueous phase. There are a small number of experimental and computational studies of glucose and Na^+ in the gas phase. Using collision-induced dissociation in the vapor phase, Heaton and Armentrout noted greater affinity of Na^+ for α- over β-glucose, although the difference was smaller than the experimental error.[41] Heaton and Armentrout also presented computational results for Na^+−glucose binding in the gas phase consistent with their experimental findings, and similar to the previously reported experimental and theoretical results of Cerda and Wesdemiotis.[42] Previous studies also include other metal ion interactions with glucose, such as Cu^+.[43] Recently, Bellesia and Gnanakaran[44] used MD simulations to examine the effect of aqueous sodium chloride on cellulose. However, to the best of our knowledge, no study has previously been published that would provide molecular-level understanding of glucose and sodium ion interactions in the aqueous phase.

In this study, we employ quantum mechanics (QM) and molecular dynamics (MD) to understand how alkali metal ions interact with aqueous glucose at the molecular level, to move toward a mechanistic understanding of the effect of inorganic salt on glucose decomposition reactions. Both α- and β-glucose isomers are considered because they are in equilibrium in aqueous solution.[21,22,41] The QM studies capture electronic structure of the glucose molecule due to the presence of a sodium ion. Thus, important features such as the oxygen lone pairs are captured, which are considered an important factor in determining energies of stable conformations of glucose.[32,45,46] The QM studies employ implicit solvent and include only the cation, as supported by the aforementioned experimental studies. The MD studies include the anion and cation as well as explicit water.

We find that there are multiple positions for Na^+ to associate with hydroxyl groups of a pyranose ring within thermal energy (k_BT) at temperatures relevant to biomass conversion in the aqueous phase. The most stable ring conformation remains the $^4C_1$ equatorial chair conformation in aqueous solution with NaCl. The presence of Na^+ perturbed the electronic structure of α-glucose to a greater extent than β-glucose, as indicated by changes in atomic partial charge. As expected, the most stable conformations allow Na^+ to associate with multiple oxygen lone pairs. Use of implicit solvent prevents quantitative agreement between QM and experimental results, presented here, for the relative energies of α- and β-glucose. However, consistency in the QM and MD results for interactions of Na^+ with hydroxyl groups provides justification for the computationally advantageous implicit solvent and for the focus on the cation only in the QM studies.

dx.doi.org/10.1021/jp409481f | J. Phys. Chem. B 2014, 118, 1990−2000

We also provide results of experimental studies to quantitatively determine the effect of NaCl on the relative populations of α- and β-glucose in aqueous solution. We found that adding NaCl to an aqueous glucose solution has very little effect on the relative populations of the epimers, while adding $CaCl_2$ increases the population of α-glucose. We discuss this result in the context of the binding preferences between the epimers and cations.

COMPUTATIONAL METHODS

QM calculations were carried out with Gaussian 09 revision C.[47] The M06-2X[48] functional was used as it has been shown to accurately estimate energy barriers, with a mean signed error of −0.98 kcal/mol for the BBH7 database,[49] and to perform well for biomolecules.[50] We employed the 6-311+G(2df,p) basis set.[51,52] Diffuse functions on hydrogen atoms were not included as they did not appreciably affect results, while diffuse functions and additional polarized functions on the non-hydrogen atoms were included to more accurately model intramolecular hydrogen bonding. The "tight" optimization convergence criteria and "ultrafine" integration grids were specified. Frequencies were scaled using factors reported by Merrick et al.[53] for the M05-2X/6-311+G(2df,p) level of theory, which is most similar to the level of theory employed here. The factors are 0.9663 for zero-point vibrational energy (ZPVE), 0.9444 for fundamental frequencies, 0.9168 for low frequencies (wavenumber less than 260 cm^{-1}), 0.9297 for enthalpy calculations, and 0.9206 for entropy calculations. All minima were verified to have zero negative frequencies. Normal mode analysis revealed that the low wavenumbers were primarily due to ring puckering and were strongly coupled. Corrections to the harmonic oscillator approximation for internal rotation were not included. The aqueous environment was modeled using the CPCM implicit solvent model[54,55] for water using UFF radii.[56] Gas-phase counterpoise corrections to basis set superposition error[57,58] were included in calculations of Na^+ binding energies. Partial charges were evaluated with the CHelpG scheme[59] and with natural population analysis (NPA)[60] using NBO 5.9.[61]

Enhanced sampling molecular dynamics simulations, specifically replica exchange molecular dynamics (REMD), were conducted to study the sodium chloride interaction with α- and β-glucose and explicit water using Gromacs 4.5.1.[62] Three sets of REMD simulations were included: a control study of glucose in water, a system with 0.9 M sodium chloride, and a system with 2.0 M sodium chloride. Table 1 shows details of the three systems. In each of the systems, two α-glucose and two β-glucose molecules are included to enhance the sampling of events of glucose with sodium or water. Such a setup is justified by our analysis shown in the Supporting Information that there is very little interglucose interaction during production runs. Each of the REMD simulations used 40 replicas and covered a temperature range of 270−505 K. The acceptance rate was 20%. Each of the replicas was simulated for 100 ns, and a total of 12 μs simulations have been done in the current study.

Table 1. Simulation Details of the Three Systems Studied with REMD

	no. of molecules				NaCl	
label	α-glucose	β-glucose	water	NaCl	% wt	M
neat	2	2	2446	0	0.0	0.0
0.9 M	2	2	2370	38	4.9	0.9
2 M	2	2	2282	82	10.3	2.0

The GLYCAM06 force field[63] parameters were used for glucose, a modified version of ion parameters[64] was used for sodium chloride, and TIP3P water model[65] was used for the explicit water molecules. Details about the REMD methods and setup process are included in a previous paper by Tian and Garcia.[66] The v-rescale thermostat was used for the temperature coupling with a coupling time constant τ_T = 1.0 ps. The glucose, solvent, and ions were coupled separately to thermostats with the same coupling parameters. van der Waals interactions were treated using a 0.1 Å cutoff. The electrostatic interactions were treated by smooth particle mesh Ewald summation with a grid size of 1.0 Å. All bond interactions involving hydrogen atoms were constrained using SETTLE[67] and LINCS[68] to allow a 2 fs integration time step.

EXPERIMENTAL METHODS

Glucose, sodium chloride, and calcium chloride (Certified ACS) were purchased from Fisher and used as received. Samples were prepared by dissolving measured amounts of glucose and salt into deionized water (18 MΩ cm) and allowing equilibration at room temperature for at least 48 h. A JASCO DIP-370 automatic polarimeter was used to measure the specific rotation of the solution using the sodium D-line (589 nm) as a light source. For each experiment, a 10 cm length tube was filled with sample and loaded into the polarimeter. A total of three measurements were taken for each sample at room temperature (22−23 °C) with the data presented herein being the average with an error of one standard deviation.

RESULTS AND DISCUSSION

QM Neat Glucose Conformations. Low-energy conformations of neat α- and β-glucose are presented in Figure 1 to provide a baseline for comparing glucose geometries in the presence of a sodium ion using the same methodology. Both structures shown are in the gg conformation, in agreement with the most stable conformation reported in most experimental studies.[25] Other low-energy conformations of neat glucose have been enumerated in previous QM studies completed in gas, implicit water, and explicit water.[29,69] The ones shown here are the lowest-energy conformations from among a variety of conformations investigated at the M06-2X/6-311+G(2df,p) level of theory and implicit solvent, including conformations from previous computational and experimental studies.[70−76] At 298 K with M06-2X/6-311+G(2df,p) and implicit solvent, the α-glucose conformation is 0.32 kcal/mol lower in Gibbs free energy than the β conformation. Experimental studies show a higher population of β-glucose than α-glucose corresponding to a few tenths of a kcal/mol.[21] The estimated error in energy difference is less than 0.75 kcal/mol, likely due to the exclusion of explicit water molecules, which have been found to be required to capture the influence of solvent on the anomeric effect.[77,78] However, the implicit solvent did capture some of the trend of a decreased α-glucose population in water as compared to in the gas phase; at 298 K with M06-2X/6-311+G(2df,p) in the gas phase, the α-glucose conformation is 0.51 kcal/mol lower in energy than the β-glucose.

QM Glucose−Na^+ Interaction. Glucose has six oxygen atoms available for interaction with Na^+. Because of the adjacent positions of these groups, there are six preferential locations for Na^+ association with glucose: between O1 and

dx.doi.org/10.1021/jp409481f | J. Phys. Chem. B 2014, 118, 1990−2000

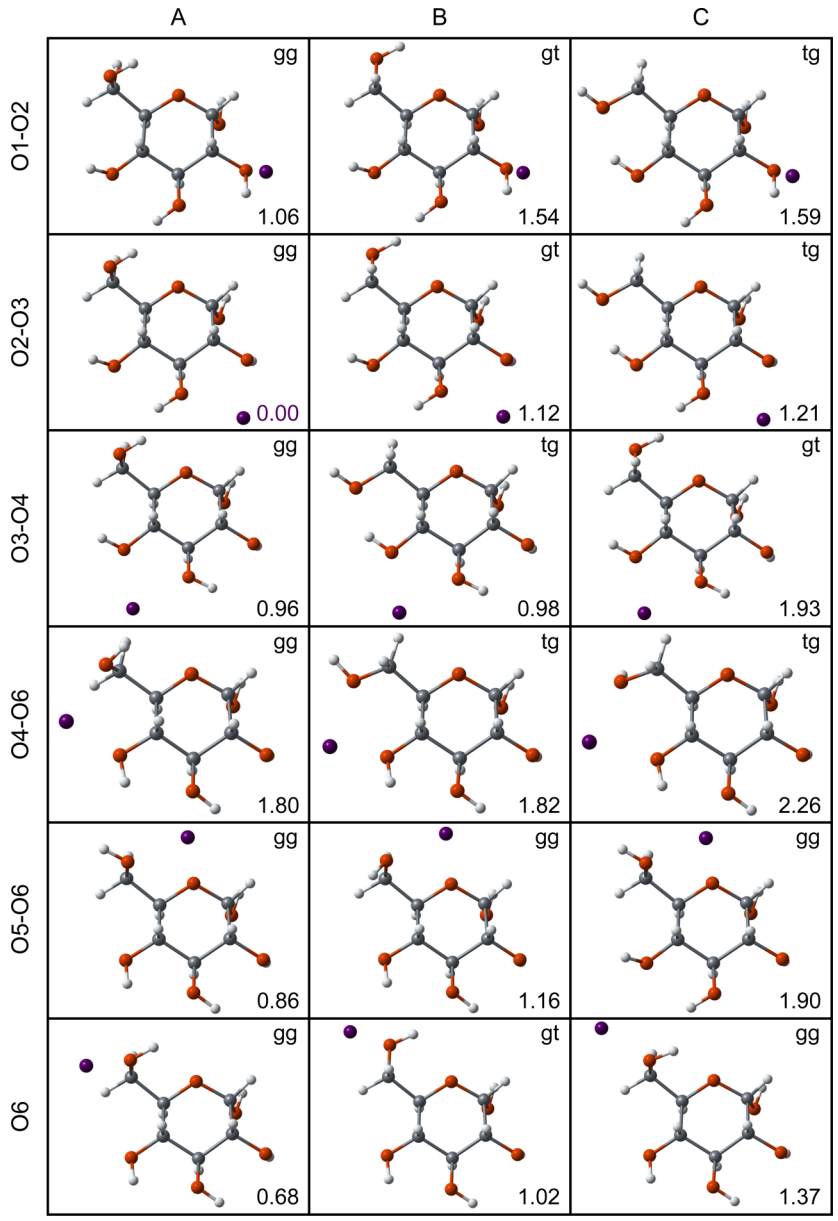


Figure 2. Low Gibbs free energy conformations of α-glucose with a sodium ion. The hydroxymethyl group orientation is denoted in the upper right-hand corner in each panel, and lower right-hand corners show the Gibbs free energy at 400 K in kcal/mol relative to the lowest energy conformation. In each of these conformations, the pyranose ring adopts an equatorial chair ($^4C_1$) geometry.

O2; O2 and O3; O3 and O4; O4 and O6; O5 and O6; or with O6 alone.

With the sodium ion in any of those positions, there are many low-energy rotamers of glucose. Figures 2 and 3 show the three lowest-energy glucose conformers found with Na^+ in each of the six preferential locations, with the orientation of the hydroxyl arm noted in the top right corner of each image. Each row has Na^+ in one location, with the lowest-energy glucose conformation for each Na^+ location on the left. The Gibbs free energy at 400 K relative to the lowest-energy conformation in each figure is noted in the bottom right corner of each conformation. This temperature is representative of the moderate temperatures employed in relevant experimental work.[15,16] Relative energies at 298 K are reported in the Supporting Information. The lowest-energy conformations of both α- and β-glucose have the hydroxymethyl group in the gg conformation. As found with neat α-glucose (see the Supporting Information), there is a low-energy tg α-glucose-Na^+ conformation approximately 1 kcal/mol higher in Gibbs free energy at 400 K than the lowest-energy gg conformation found. The lowest-energy gt conformation for neat α-glucose is just 0.2 kcal/mol higher in Gibbs free energy at 400 K than the lowest-energy gg conformation, whereas the lowest-energy gt conformation for α-glucose−Na^+ is also approximately 1 kcal/mol higher in Gibbs free energy. For β-glucose, there is also a neat gt conformation 0.2 kcal/mol higher in Gibbs free energy at 400 K than the lowest-energy neat gg conformation, but 1 kcal/mol higher in energy with Na^+ present. Unlike α-glucose−Na^+, β-glucose−Na^+ has a tg conformation only 0.5 kcal/mol higher in energy than the lowest-energy gg conformation, whereas the lowest-energy neat β-glucose tg conformation found is approximately 2 kcal/mol higher in energy than gg. These results indicate that gg remains a favorable conformation of the hydroxymethyl group for both α- and β-glucose when

dx.doi.org/10.1021/jp409481f | J. Phys. Chem. B 2014, 118, 1990−2000

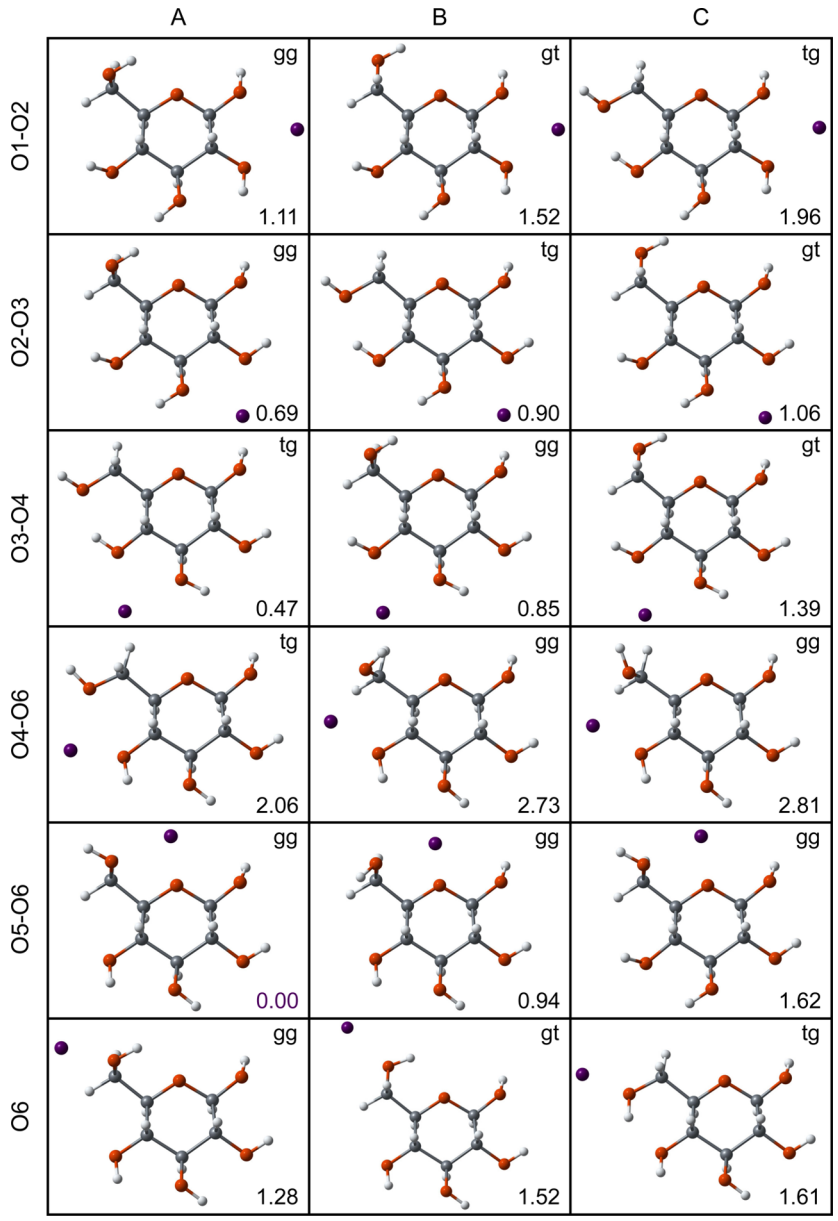


Figure 3. Low Gibbs free energy conformations of β-glucose with a sodium ion. The hydroxymethyl group orientation is denoted in the upper right-hand corner in each panel, and lower right-hand corners show the Gibbs free energy at 400 K in kcal/mol relative to the lowest energy conformation. In each of these conformations, the pyranose ring adopts an equatorial chair ($^4C_1$) geometry.

Na^+ is present, while the relative populations of gt and tg are perturbed, with gt comprising less of the population for both α- and β-glucose and the tg conformation of β-glucose becoming more abundant. For both anomers, with or without Na^+ present, the hydrogen of the O1 hydroxyl group is oriented toward the O5 ring oxygen in the low-energy conformations, even when Na^+ associates with O5.

All of the α-glucose−Na^+ conformations shown in Figure 2 are in the $^4C_1$ equatorial chair conformation and have Gibbs free energies within 2.3 kcal/mol of each other. The β-glucose−Na^+ conformations shown in Figure 3 are within 2.8 kcal/mol of each other. Distances between Na^+ and each oxygen atom are included in the Supporting Information.

With a sodium ion, the α-glucose conformation with the lowest identified Gibbs free energy is 0.23 kcal/mol lower in energy than the lowest identified Gibbs free energy conformation of β-glucose at 400 K, and 0.39 kcal/mol lower at 298 K. This is a minor shift in favor of the α-glucose epimer; without Na^+, α-glucose is 0.17 kcal/mol lower in energy than β-glucose at 400 K, and 0.32 at 298 K. While this is not a significant perturbation in the relative energies of the epimers, it is consistent with a small Na^+ binding preference for α-glucose. Specifically, the calculated binding enthalpy of Na^+ with α-glucose is −5.2 kcal/mol at 298 K, while it is −5.0 kcal/mol at 298 K for β-glucose. As previously noted, we do not expect this implicit solvent system to fully capture the influence of solvent, but it does reflect experimental trends in terms of the shift toward the β anomer moving from gas phase to solvent.

The QM results allow us to examine perturbations in glucose's atomic structure. C−C and C−O bond lengths and partial charges on C and O according to NPA and CHelpG schemes are included in the Supporting Information. The presence of Na^+ only slightly changes the C−C and C−O bond distances. The maximum such bond length difference between

dx.doi.org/10.1021/jp409481f | J. Phys. Chem. B 2014, 118, 1990−2000

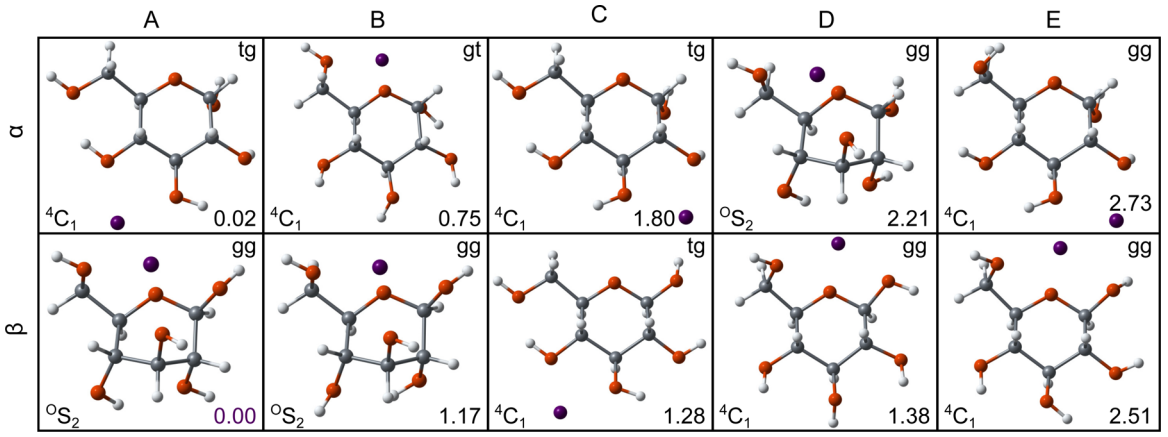


Figure 4. Low Gibbs free energy conformations of α- and β-glucose−Na^+ complexes from M06-2X/6-311+G(2df,p) calculations in the gas phase. The annotations display the orientation of the hydroxymethyl group, ring pucker, and Gibbs free energy at 400 K relative to the lowest-energy conformation found.

the lowest-energy neat α-glucose structure in Figure 1 and the low-energy α-glucose-Na^+ structures in Figure 2 is 0.009 Å. Between the β-glucose structure in Figure 1 and the low-energy β-glucose−Na^+ structures in Figure 3, the maximum difference is 0.011 Å. For perspective, the maximum such difference between the neat α- and β-glucose C−C and C−O bond lengths is 0.16 Å, due to the different C1−O1 bond lengths.

There is a notable difference in partial charge on some C and O atoms for α-glucose in the presence of Na^+. For reference, the Supporting Information includes two additional conformations of neat α- and β-glucose that are within 1.0 kcal/mol of the conformations shown in Figure 1. Comparing just three low-energy neat α-glucose conformations shows a variation in CHelpG partial charge on carbon atoms of up to 0.32 au and on oxygen atoms of up to 0.21 au The NPA scheme shows a variation of 0.00 au on carbon atoms and 0.01 au on oxygen atoms. Comparing the lowest-energy conformations of neat α-glucose and α-glucose with Na^+, when Na^+ is present the CHelpG scheme attributes 0.38 au more negative charge to O5 (CHelpG partial charge of −0.77 au) and 0.22 au less negative charge to O1 (CHelpG partial charge of −0.44 au). These differences are outside the variation seen among the three low-energy rotamers of neat α-glucose. Notably, while the NPA scheme showed at most 0.01 au difference in partial charges for O and C among the neat α-glucose rotamers, when Na^+ is present it attributes an increased negative partial charge of 0.14 au to O5 (NPA partial charge of −0.78 au) and 0.15 au less negative charge to O1 (NPA partial charge of −0.64 au), with a perturbation of only 0.01 au for the carbon atoms.

The perturbation of β-glucose atomic partial charges with a Na^+ ion is less pronounced. For neat β-glucose, the variation among the three low-energy rotamers shown is 0.36 au for carbon atoms and 0.16 au for oxygen atoms according to the CHelpG scheme, with the largest variation seen for C4 and O5 and significant variation also shown for C1, C2, and C3. The NPA scheme quantified differences of at most 0.01 au. Comparing the lowest-energy conformations found for β-glucose with and without Na^+, the difference in CHelpG partial charges is less than the variation seen among three low-energy rotamers of neat β-glucose (see the Supporting Information). The largest difference from the NPA scheme is just 0.04 au for O6. As mentioned above, the full CHelpG and NPA partial charges for non-hydrogen atoms of all structures shown are provided in the Supporting Information.

It is interesting to consider the greater effect of Na^+ on α-glucose versus β-glucose in the context of Angyal's assertion that metals interact more strongly with sugars that contain adjacent axial and equatorial hydroxyl groups.[37] Angyal specifically credited an axial−equatorial−axial arrangement of adjacent hydroxyl groups for effective sugar−cation binding. Neither α- or β-glucose−Na^+ molecules have that particular arrangement. The low-energy conformations in Figures 2 and 3 all contain rings in the $^4C_1$ conformation. All β-glucose hydroxyl groups are thus in an equatorial arrangement. The α-glucose O1 is axial and adjacent to the equatorial O2, thus containing part of that axial−equatorial−axial arrangement. Adjacent axial and equatorial hydroxyl groups have shorter distances between the oxygen atoms than do adjacent equatorial−equatorial hydroxyl groups, which can increase intramolecular hydrogen bonding. For example, the distance for the lowest-energy α-glucose−Na^+ conformation shown in Figure 2 is 2.72 Å for O1−O2 and 2.32 Å for O1−HO2, while for the lowest-energy β-glucose−Na^+ conformation shown in Figure 3, it is 2.85 Å for O1−O2 and 2.57 Å for O1−HO2. The shorter O1−O2 and O1−HO2 distances for α-glucose allow for more electron donation from O1, as evidenced by the less-negative partial charge on O1.

As noted above, the low-energy conformations found for α- and β-glucose−Na^+ are $^4C_1$ (equatorial chair) ring conformations. Our search for low-energy conformations also included different puckered ring conformations.[79] Some low-energy boat-like and axial-chair ($^1C_4$) conformations are shown in the Supporting Information, with their IUPAC puckering designation noted.[80,81] With implicit water, geometries not in the equatorial chair conformation are 4.3 kcal/mol or more higher in energy at 400 K than the lowest $^4C_1$ conformations for α-glucose, and 6.0 kcal/mol or more higher for β-glucose. The results suggest that the lower energy of the α-glucose−Na^+ puckered conformations as compared to β-glucose−Na^+ puckered conformations is due to more O−HO interaction available to the α anomer. For example, in the lowest-energy α-glucose−Na^+ puckered geometry shown, two hydroxyl hydrogen atoms are oriented toward a hydroxyl oxygen (HO4−O2 and HO2−O1), while only one such orientation is available to the lowest-energy β-glucose−Na^+ puckered geometry shown (HO4−O2). The additional interactions are directly due to the cis orientation of O1 and O2 of α-glucose.

dx.doi.org/10.1021/jp409481f | J. Phys. Chem. B 2014, 118, 1990−2000

The lack of lower-energy puckered conformations contrasts with results in gas phase previously reported by Heaton and Armentrout.[41] They detailed five low-energy conformations each for "sodium-bound" α- and β-glucose optimized at the B3LYP/6-311+G(d,p) level of theory in the gas phase. While some of the conformations are similar to those included in Figures 2 and 3, one of the low-energy α-glucose−Na^+ conformations in the gas phase is reported to be in the $^{O,3}B$ boat conformation. For β-glucose−Na^+, two of the five low-energy conformations reported in the gas phase are noted to be in the $^{O,3}B$ boat conformation, including the lowest-energy conformation. To verify that the difference in results is due to the different environment, we repeated our optimizations in the gas phase with the same level of theory used for the implicit solvent calculations, M06-2X/6-311+G(2df,p). Our gas-phase results are similar to those reported by Heaton and Armentrout. We also found a low-energy nonchair conformation of α-glucose, and the lowest Gibbs free energy conformation for β-glucose we found was a nonchair conformation. The five lowest-energy, nonchair conformations found for both α- and β-glucose−Na^+ in the gas phase are shown in Figure 4.

The different gas-phase and implicit solvent results are expected. Without implicit solvent, the sodium ion and oxygen lone pairs are not shielded as they would be in an aqueous environment. Thus, in the gas phase, in some configurations the higher energy due to ring distortion is balanced by the extent that it allows greater interaction between the electron-poor Na^+ and the electron-rich oxygen lone pairs. In implicit solvent, these interactions are shielded, and greater separation in charge is stabilized by the dielectric constant of the continuum model.

MD Simulations. In this section, we compare the QM results for glucose with Na^+ in implicit solvent to results of molecular dynamics simulations that examine glucose in explicit solvent with or without NaCl present. This allows us to check how QM results for glucose conformations with Na^+ in implicit solvent might be different given the opportunity for explicit interactions with solvent molecules or with the anion. Note that the MD force field used chose to average properties of α- and β-glucose anomers to provide general, widely applicable parameters.[63] Consequently, we do not expect the MD simulations completed here to capture fine-grained differences between the behaviors of the anomers. However, the MD system provides valuable information about the interaction of the glucose molecules and the solvent environment. Details of the α-glucose results are presented in the Supporting Information, and β-glucose results are presented here.

One of the questions of interest is whether the cation associates with glucose to a greater extent than does the anion. The radial distribution functions (RDF) of sodium and chloride ions with respect to different β-glucose oxygen atoms are plotted in Figure 5. The RDF peaks for Na^+ are located at approximately 2.4 Å, which agrees with QM calculations (see O−Na^+ distances in the Supporting Information). The peak of the RDF for Cl^- distance to glucose oxygens is located at 3.2 Å, consistent with Cl^- interaction with hydrogen atoms. Importantly, the height of the Cl−O peak is much lower than for Na^+, at about 1.5 versus 5 for Na^+−O, indicating very weak interactions. This small affinity of chloride ions to the heavy atoms of glucose justifies our neglecting chloride ions in our QM calculations and is consistent with experimental observations of the lower impact of chloride ions.[14]

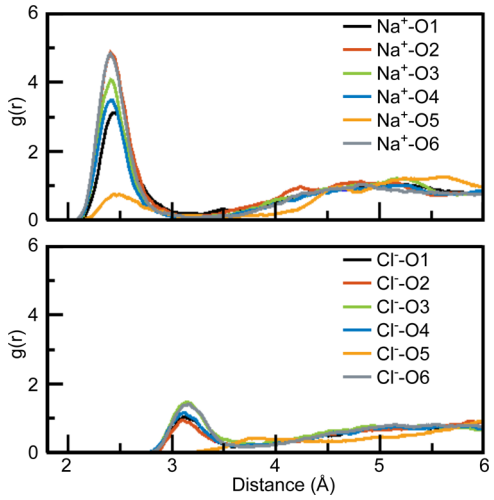


Figure 5. Radial distribution function of sodium and chloride ions with respect to different oxygen atoms for β-glucose, from the simulation with 0.9 M NaCl.

A key question for the MD simulations is whether the QM findings of Na^+ simultaneous association with multiple oxygens were due only to the lack of competing interactions with solvent, or, as Angyal proposed, Na^+ associates with more than one hydroxyl group when possible.[38] Figure 6 shows the RDF

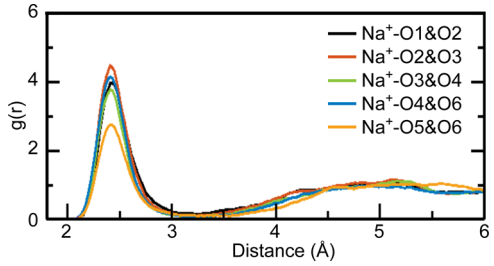


Figure 6. Radial distribution function of sodium ions with respect to different combinations of two oxygen atoms for β-glucose, from the simulation with 0.9 M NaCl.

of sodium affinity to different combinations of two oxygen atoms. As with the RDF for single oxygen atoms, the peak of the RDFs is located at 2.4 Å, with the strongest affinity for Na^+ to sit at the "bridging" position between the O2 and O3 oxygen atoms, followed by O4−O6 and O1−O2. From the QM results, the lowest-energy position for Na^+ associated with β-glucose is bridging between O5 and O6. We do expect differences in the QM and MD results due to the fixed partial charges in the MM force fields, which contrast with QM findings of partial charges, as well as the different solvent treatments. Importantly, the RDF peaks in Figure 6 indicate an affinity for Na^+ to interact with two glucose oxygen atoms simultaneously even when explicit solvent molecules are present, consistent with Angyal's hypothesis.

Polarimetry Results. The Raman spectroscopy results presented by Franks et al. suggest that alkali and alkaline earth metals bind to the different anomers of glucose with different strengths, resulting in a shift in relative populations of the two anomers when inorganic salts are added to aqueous glucose solutions.[40] Their spectra comparison provides qualitative evidence of population shift. The light polarimetry results presented here provide quantitative data on the extent of the

dx.doi.org/10.1021/jp409481f | J. Phys. Chem. B 2014, 118, 1990−2000

population shift, shown in Figure 7. The observed percent of α-glucose in aqueous solution without salt added is similar to

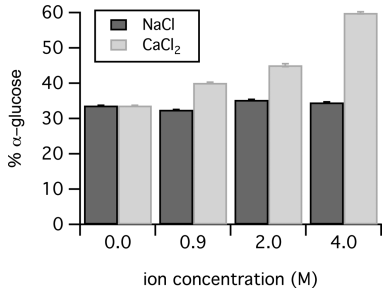


Figure 7. Percent of glucose in the α conformation in 1 M aqueous glucose solutions with varying amounts of NaCl (dark gray) or $CaCl_2$ (light gray).

values previously reported by Angyal[21] and by Zhu et al.[22] The significant result is the difference in direction of the change in α-glucose population due to the addition of either NaCl or $CaCl_2$ and the difference in magnitude of the change. As more $CaCl_2$ is added to the aqueous glucose solution, the population of α-glucose increases. However, no significant change is observed for NaCl, despite both Ca^{2+} and Na^+ being positively charged.

The effect of $CaCl_2$ on the anomer populations is consistent with the study by Franks et al.[40] For the population to change due to $CaCl_2$ addition but not NaCl, the magnitude of the difference in binding energy for the different anomers would need to be greater for Ca^{2+} than for Na^+. As noted above, the QM results show an α-glucose−Na^+ binding enthalpy of approximately −5.2 kcal/mol, just slightly greater (and within the method's expected error) than the β-glucose−Na^+ binding enthalpy of −5.0 kcal/mol. To provide a comparison of those binding energies to anomer binding energies with Ca^{2+}, we performed fully relaxed optimizations on all of the structures in Figures 2 and 3, exchanging the sodium ion for a calcium ion. Using the same level of theory (M06-2X/6-311+G(2df,p) with implicit water solvent at 25 °C), we found a binding enthalpy of −12.5 kcal/mol for Ca^{2+} interaction with α-glucose, and a binding enthalpy of −11.3 kcal/mol for β-glucose. These preliminary values show a greater binding magnitude, which is expected for the divalent ion versus the monovalent ion. Notably, the difference in interaction between the anomers is greater for Ca^{2+} (1.2 kcal/mol, instead of 0.2 kcal/mol). The stronger affinity of Ca^{2+} for α-glucose is consistent with perturbing the equilibrium toward that isomer. The literature on the anomeric effect offers a further suggestion of why we do not observe an increase in α-glucose in the presence of NaCl. As noted in the Introduction, the population of α-glucose is a function of the polarity of the solvent, with its ratio decreasing as polarity increases. While the addition of salt decreases the polarity of water in the bulk, in the immediate cluster around the salt ions, the water dipole moment may be increased.[82] The increase of the polarity of the cluster may offset a slight Na^+ binding affinity for α-glucose. The results published by Franks et al.[40] also show a markedly smaller effect from NaCl than from $CaCl_2$, consistent with the experimental results shown here. While the spectrum Franks et al. reported from the sample with NaCl is different than the neat sample, the shift is quite subtle. Thus, the quantitative results from light polarimetry shown here provide valuable additional information.

CONCLUSIONS

Inorganic salts are natural components of biomass and have been shown to affect glucose conversion reactions such as increasing the yield of HMF.,[11−16] They are also present in biological aqueous systems, and Na^+−glucose interactions have important physiological roles.[17−19] Understanding the interactions of these salts provides a foundation for future mechanistic studies of how these salts affect reactions and biological function. This information could provide valuable data for mechanistic models of glucose decomposition, enzyme modeling, and rational catalyst design.

In this study, both the QM and the MD results show affinity between the sodium ion and the glucose oxygen atoms, in line with experimental evidence for the formation of glucose−salt complexes.[16,38] MD simulations with explicit water and including the counterion, Cl^-, confirm the hypothesis that the cation has a stronger effect than the anion on glucose. The similarities between the QM results with implicit water and MD results with explicit water provide confidence in the ability of the implicit water model to capture the Na^+−glucose behavior in water. The MD results show that even in the presence of solvent molecules, sodium ions display an affinity to sit between two glucose oxygen atoms, as found in the QM study with implicit water. The comparison to previous gas-phase studies shows that the inclusion of the solvent electrostatic environment significantly improves its agreement with simulations using explicit water. A significant finding of this study is that there are many low-energy conformations of α- and β-glucose−Na^+ complexes. Future studies to elucidate mechanistic effects of cations on glucose reactions will need to ensure adequate sampling of both glucose rotamers and different cation positions.

The QM calculations allowed examination of how Na^+ perturbs glucose structure. The effects on β-glucose electronic structure due to the presence of Na^+, as indicated by perturbations of atomic partial charge, are similar to perturbations seen among different rotamers of neat β-glucose. In contrast, for α-glucose, the presence of Na^+ decreased the magnitude of the negative partial charge on O1 and increased the negative charge on O5. The closer proximity of O1−O2 in α-glucose likely allows more electron donation. Despite the different effects on partial charge, there is little preference for Na^+ to interact with one anomer over the other. Experimental studies quantified the effect on anomer populations of adding NaCl to an aqueous glucose solution, confirming the finding that Na^+ does not significantly perturb the anomer populations. This behavior is in contrast to the observed marked population shift toward more α-glucose upon addition of $CaCl_2$. QM results show that not only does the divalent ion bind more strongly to glucose than the monovalent ion, it preferentially binds to α-glucose over β-glucose. The preference toward α-glucose may be due to the closer proximity of the O1 and O2 oxygens to each other, which allows more electron donation, evidenced by perturbations of the α-glucose O1 partial charge when interacting with the positive ions. This work suggests that part of the observed effects of inorganic salts on glucose reaction products could be due to shifts in equilibrium ratios, when salt employed causes such as shift, or due to selective redistribution of electronic density. Such hypotheses could be tested in future QM studies.

dx.doi.org/10.1021/jp409481f | J. Phys. Chem. B 2014, 118, 1990−2000

■ ASSOCIATED CONTENT

Supporting Information

Complete ref 47; additional low-energy conformations of neat α- and β-glucose in implicit water; non-$^4C_1$ conformations of α- and β-glucose with Na^+; C−C and C−O bond distances for QM structures in implicit water; C and O partial charges for QM structures in implicit water; MD results for hydroxymethyl orientation and ring conformation and comparing α- and β-glucose simulation results; and atomic coordinates for all QM structures. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: gnana@lanl.gov.

*E-mail: broadbelt@northwestern.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Advanced Biofuels Consortium (NABC), which is funded by the Department of Energy (DOE) Office of Energy Efficiency and Renewable Energy (EERE) through the Office of Biomass Program, grant number DE-EE0003044. This research used computational resources of the National Energy Research Scientific Computing Center, which is supported by the Office of Science of the U.S. DOE under Contract No. DE-AC02-05CH11231; NREL Computational Sciences Center supported by the DOE Office of EERE under Contract No. DE-AC36-08GO28308; as well as by CNLS and LANL Institutional Computing. H.B.M. thanks Chris Mayes for helpful scripts. H.B.M. was supported by the DOE Computational Science Graduate Fellowship (CSGF), which is provided under grant number DE-FG02-97ER25308, and the ARCS Foundation Inc., Chicago Chapter.

■ REFERENCES

(1) Zugenmaier, P. *Crystalline Cellulose and Derivatives: Characterization and Structures*; Springer-Verlag: Berlin Heidelberg, 2008; Chapter 1.

(2) Steen, E. J.; Kang, Y.; Bokinsky, G.; Hu, Z.; Schirmer, A.; McClure, A.; del Cardayre, S. B.; Keasling, J. D. Microbial Production of Fatty-Acid-Derived Fuels and Chemicals from Plant Biomass. *Nature* **2010**, *463*, 559−562.

(3) Alonso, D. M.; Bond, J. Q.; Dumesic, J. A. Catalytic Conversion of Biomass to Biofuels. *Green Chem.* **2010**, *12*, 1493−1513.

(4) Bozell, J. J.; Petersen, G. R. Technology Development for the Production of Biobased Products from Biorefinery Carbohydrates−the US Department of Energy's "Top 10" Revisited. *Green Chem.* **2010**, *12*, 539−554.

(5) Climent, M. J.; Corma, A.; Iborra, S. Converting Carbohydrates to Bulk Chemicals and Fine Chemicals over Heterogeneous Catalysts. *Green Chem.* **2011**, *13*, 520−540.

(6) Gallezot, P. Conversion of Biomass to Selected Chemical Products. *Chem. Soc. Rev.* **2012**, *41*, 1538−1558.

(7) Román-Leshkov, Y.; Barrett, C. J.; Liu, Z. Y.; Dumesic, J. A. Production of Dimethylfuran for Liquid Fuels from Biomass-Derived Carbohydrates. *Nature* **2007**, *447*, 982−985.

(8) Huang, R.; Qi, W.; Su, R.; He, Z. Integrating Enzymatic and Acid Catalysis to Convert Glucose into 5-Hydroxymethylfurfural. *Chem. Commun.* **2010**, *46*, 1115−1117.

(9) Zhao, H.; Holladay, J. E.; Brown, H.; Zhang, Z. C. Metal Chlorides in Ionic Liquid Solvents Convert Sugars to 5-Hydroxymethylfurfural. *Science* **2007**, *316*, 1597−1600.

(10) Chidambaram, M.; Bell, A. T. A Two-Step Approach for the Catalytic Conversion of Glucose to 2,5-Dimethylfuran in Ionic Liquids. *Green Chem.* **2010**, *12*, 1253−1262.

(11) Mohan, D.; Pittman, C. U., Jr.; Steele, P. H. Pyrolysis of Wood/Biomass for Bio-oil: A Critical Review. *Energy Fuels* **2006**, *20*, 848−889.

(12) Patwardhan, P. R.; Satrio, J. A.; Brown, R. C.; Shanks, B. H. Product Distribution from Fast Pyrolysis of Glucose-Based Carbohydrates. *J. Anal. Appl. Pyrolysis* **2009**, *86*, 323−330.

(13) Patwardhan, P. R.; Satrio, J. A.; Brown, R. C.; Shanks, B. H. Influence of Inorganic Salts on the Primary Pyrolysis Products of Cellulose. *Bioresour. Technol.* **2010**, *101*, 4646−4655.

(14) Rasrendra, C. B.; Makertihartha, I. G. B. N.; Adisasmito, S.; Heeres, H. J. Green Chemicals from D-Glucose: Systematic Studies on Catalytic Effects of Inorganic Salts on the Chemo-Selectivity and Yield in Aqueous Solutions. *Top. Catal.* **2010**, *53*, 1241−1247.

(15) Hansen, T. S.; Mielby, J.; Riisager, A. Synergy of Boric Acid and Added Salts in the Catalytic Dehydration of Hexoses to 5-Hydroxymethylfurfural in Water. *Green Chem.* **2011**, *13*, 109−114.

(16) Combs, E.; Cinlar, B.; Pagan-Torres, Y.; Dumesic, J. A.; Shanks, B. H. Influence of Alkali and Alkaline Earth Metal Salts on Glucose Conversion to 5-Hydroxymethylfurfural in an Aqueous System. *Catal. Commun.* **2013**, *30*, 1−4.

(17) Karpowich, N. K.; Wang, D.-N. Structural Biology. Symmetric Transporters for Asymmetric Transport. *Science* **2008**, *321*, 781−782.

(18) Leturque, A.; Brot-Laroche, E.; Le Gall, M. GLUT2 Mutations, Translocation, and Receptor Function in Diet Sugar Managing. *Am. J. Physiol.: Endocrinol. Metab.* **2009**, *296*, E985−E992.

(19) Zeuthen, T.; MacAulay, N. Transport of Water Against Its Concentration Gradient: Fact or Fiction? *WIREs Membr. Transp. Signaling* **2012**, *1*, 373−381.

(20) Li, J.; Shaikh, S. A.; Enkavi, G.; Wen, P.-c.; Huang, Z.; Tajkhorshid, E. Transient Formation of Water-Conducting States in Membrane Transporters. *Proc. Natl. Acad. Sci. U.S.A.* **2013**, *110*, 7696−7701.

(21) Angyal, S. J. The Composition and Conformation of Sugars in Solution. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 157−166.

(22) Zhu, Y.; Zajicek, J.; Serianni, A. S. Acyclic Forms of [1−^{13}C] Aldohexoses in Aqueous Solution: Quantitation by ^{13}C NMR and Deuterium Isotope Effects on Tautomeric Equilibria. *J. Org. Chem.* **2001**, *66*, 6244−6251.

(23) Bock, K.; Duus, J. Ø. A Conformational Study of Hydroxymethyl Groups in Carbohydrates Investigated by ^{1}H NMR Spectroscopy. *J. Carbohydr. Chem.* **1994**, *13*, 513−543.

(24) Thibaudeau, C.; Stenutz, R.; Hertz, B.; Klepach, T.; Zhao, S.; Wu, Q.; Carmichael, I.; Serianni, A. S. Correlated C-C and C-O Bond Conformations in Saccharide Hydroxymethyl Groups: Parametrization and application of redundant ^{1}H-^{1}H, ^{13}C-^{1}H, and ^{13}C-^{13}C NMR J-couplings. *J. Am. Chem. Soc.* **2004**, *126*, 15668−15685.

(25) Mason, P. E.; Neilson, G. W.; Enderby, J. E.; Saboungi, M.-L.; Cuello, G.; Brady, J. W. Neutron Diffraction and Simulation Studies of the Exocyclic Hydroxymethyl Conformation of Glucose. *J. Chem. Phys.* **2006**, *125*, 224505.

(26) Brady, J. W. Molecular Dynamics Simulations of α-D-Glucose in Aqueous Solution. *J. Am. Chem. Soc.* **1989**, *111*, 5155−5165.

(27) Barnett, C. B.; Naidoo, K. J. Stereoelectronic and Solvation Effects Determine Hydroxymethyl Conformational Preferences in Monosaccharides. *J. Phys. Chem. B* **2008**, *112*, 15450−15459.

(28) Cramer, C. J.; Truhlar, D. G.; French, A. D. Exo-anomeric Effects on Energies and Geometries of Different Conformations of Glucose and Related Systems in the Gas Phase and Aqueous Solution. *Carbohydr. Res.* **1997**, *298*, 1−14.

(29) Barrows, S. E.; Storer, J. W.; Cramer, C. J.; French, A. D.; Truhlar, D. G. Factors Controlling Relative Stability of Anomers and Hydroxymethyl Conformers of Glucopyranose. *J. Comput. Chem.* **1998**, *19*, 1111−1129.

(30) Molteni, C.; Parrinello, M. Glucose in Aqueous Solution by First Principles Molecular Dynamics. *J. Am. Chem. Soc.* **1998**, *7863*, 2168−2171.

(31) Juaristi, E.; Cuevas, G. Recent Studies of the Anomeric Effect. *Tetrahedron* **1992**, *48*, 5019−5087.
(32) Kirby, A. J.; William, N. H. In *The Anomeric Effect and Associated Stereoelectronic Effects*; Thatcher, G. R. J., Ed.; American Chemical Society: Washington, DC, 1993; Chapter 4, pp 55−69.
(33) Eliel, E. L.; Giza, C. A. Conformational Analysis. XVII. 2-Alkoxy- and 2-Alkylthiotetrahydropyrans and 2-Alkoxy-1,3-dioxanes. Anomeric effect. *J. Org. Chem.* **1968**, *33*, 3754−3758.
(34) Calloud, M. Sur la Combinaison du Chlorure de Sodium avec le Sucre de Diabétes et Celui de Raisin. *J. Pharm.* **1825**, *11*, 562−564.
(35) Culeddu, N.; Chessa, M.; Porcu, M. C.; Fresu, P.; Tonolo, G.; Virgilio, G.; Migaleddu, V. NMR-Based Metabolomic Study of Type 1 Diabetes. *Metabolomics* **2012**, *8*, 1162−1169.
(36) Ali, K.; Maltese, F.; Fortes, A. M.; Pais, M. S.; Verpoorte, R.; Choi, Y. H. Pre-Analytical Method for NMR-based Grape Metabolic Fingerprinting and Chemometrics. *Anal. Chim. Acta* **2011**, *703*, 179−186.
(37) Angyal, S. J. Sugar-Cation Complexes-Structure and Applications. *Chem. Soc. Rev.* **1980**, *9*, 415−428.
(38) Angyal, S. J. Complexes of Metal Cations with Carbohydrates in Solution. *Adv. Carbohydr. Chem. Biochem.* **1989**, *47*, 1−43.
(39) Frahn, J. L.; Mills, J. A. Paper Ionophoresis of Carbohydrates. I. Procedures and Results for Four Electrolytes. *Aust. J. Chem.* **1959**, *12*, 65−89.
(40) Franks, F.; Hall, J. R.; Irish, D. E.; Norris, K. The Effect of Cations on the Anomeric Equilibrium of D-Glucose in Aqueous Solutions—A Raman-Spectral Study. *Carbohydr. Res.* **1986**, *157*, 53−64.
(41) Heaton, A. L.; Armentrout, P. B. Experimental and Theoretical Studies of Sodium Cation Interactions with D-Arabinose, Xylose, Glucose, and Galactose. *J. Phys. Chem. A* **2008**, *112*, 10156−10167.
(42) Cerda, B. A.; Wesdemiotis, C. Thermochemistry and Structures of Na^+ Coordinated Mono- and Disaccharide Stereoisomers. *Int. J. Mass Spectrom.* **1999**, *189*, 189−204.
(43) Alcamí, M.; Luna, A.; Mó, O.; Yáñez, M.; Boutreau, L.; Tortajada, J. Experimental and Theoretical Investigation of the Reactions between Glucose and Cu^+ in the Gas Phase. *J. Phys. Chem. A* **2002**, *106*, 2641−2651.
(44) Bellesia, G.; Gnanakaran, S. Sodium Chloride Interaction with Solvated and Crystalline Cellulose: Sodium Ion Affects the Cellotetraose Molecule and the Cellulose Fibril in Aqueous Solution. *Cellulose* **2013**, *20*, 2695−2702.
(45) Edward, J. T. Stability of Glycosides to Acid Hydrolysis: A Conformational Analysis. *Chem. Ind.* **1955**, 1102−1104.
(46) Salzner, U.; Schleyer, P. v. R. Ab Initio Examination of Anomeric Effects in Tetrahydropyrans, 1,3-Dioxanes, and Glucose. *J. Org. Chem.* **1994**, *59*, 2138−2155.
(47) Frisch, M. J.; et al. *Gaussian 09*, revision C.01; Gaussian, Inc.: Wallingford, CT, 2010.
(48) Zhao, Y.; Truhlar, D. G. The M06 Suite of Density Functionals for Main Group Thermochemistry, Thermochemical Kinetics, Noncovalent Interactions, Excited States, and Transition Elements: Two New Functionals and Systematic Testing of Four M06-Class Functionals and 12 Other Functionals. *Theor. Chem. Acc.* **2008**, *120*, 215−241.
(49) Zhao, Y.; Truhlar, D. G. Exploring the Limit of Accuracy of the Global Hybrid Meta Density Functional for Main-Group Thermochemistry, Kinetics, and Noncovalent Interactions. *J. Chem. Theory Comput.* **2008**, *4*, 1849−1868.
(50) Sameera, W. M. C.; Pantazis, D. A. A Hierarchy of Methods for the Energetically Accurate Modeling of Isomerism in Monosaccharides. *J. Chem. Theory Comput.* **2012**, *8*, 2630−2645.
(51) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. Self-Consistent Molecular Orbital Methods. XX. A Basis Set for Correlated Wave Functions. *J. Chem. Phys.* **1980**, *72*, 650−654.
(52) Frisch, M. J.; Pople, J. A.; Binkley, J. S. Self-Consistent Molecular Orbital Methods 25. Supplementary Functions for Gaussian Basis Sets. *J. Chem. Phys.* **1984**, *80*, 3265−3269.
(53) Merrick, J. P.; Moran, D.; Radom, L. An Evaluation of Harmonic Vibrational Frequency Scale Factors. *J. Phys. Chem. A* **2007**, *111*, 11683−11700.
(54) Barone, V.; Cossi, M. Quantum Calculation of Molecular Energies and Energy Gradients in Solution by a Conductor Solvent Model. *J. Phys. Chem. A* **1998**, *102*, 1995−2001.
(55) Cossi, M.; Rega, N.; Scalmani, G.; Barone, V. Energies, Structures, and Electronic Properties of Molecules in Solution with the C-PCM Solvation Model. *J. Comput. Chem.* **2003**, *24*, 669−681.
(56) Rappé, A. K.; Casewit, C. J.; Colwell, K. S.; Goddard, W. A., III; Skiff, W. M. UFF, a Full Periodic Table Force Field for Molecular Mechanics and Molecular Dynamics Simulations. *J. Am. Chem. Soc.* **1992**, *114*, 10024−10035.
(57) Boys, S. F.; Bernardi, F. The Calculation of Small Molecular Interactions by the Differences of Separate Total Energies. Some Procedures with Reduced Errors. *Mol. Phys.* **1970**, *19*, 553−566.
(58) Simon, S.; Duran, M.; Dannenberg, J. J. How Does Basis Set Superposition Error Change the Potential Surfaces for Hydrogen-Bonded Dimers? *J. Chem. Phys.* **1996**, *105*, 11024−11031.
(59) Breneman, C. M.; Wiberg, K. B. Determining Atom-Centered Monopoles from Molecular Electrostatic Potentials. The Need for High Sampling Density in Formamide Conformational Analysis. *J. Comput. Chem.* **1990**, *11*, 361−373.
(60) Reed, A. E.; Weinstock, R. B.; Weinhold, F. Natural Population Analysis. *J. Chem. Phys.* **1985**, *83*, 735−746.
(61) Glendening, E.; Badenhoop, J. K.; Reed, A. E.; Carpenter, J. E.; Bohmann, J. A. Morales, C. M.; Weinhold, F. *NBO 5.9*; Theoretical Chemistry Institute: Madison, WI, 2011.
(62) Hess, B.; Kutzner, C.; van der Spoel, D.; Lindahl, E. GROMACS 4: Algorithms for Highly Efficient, Load-Balanced, and Scalable Molecular Simulation. *J. Chem. Theory Comput.* **2008**, *4*, 435−447.
(63) Kirschner, K. N.; Yongye, A. B.; Tschampel, S. M.; González-Outeiriño, J.; Daniels, C. R.; Foley, B. L.; Woods, R. J. GLYCAM06: A Generalizable Biomolecular Force Field. Carbohydrates. *J. Comput. Chem.* **2008**, *29*, 622−655.
(64) Joung, I. S.; Cheatham, T. E., III. Determination of Alkali and Halide Monovalent Ion Parameters for Use in Explicitly Solvated Biomolecular Simulations. *J. Phys. Chem. A* **2008**, *112*, 9020−9041.
(65) Jorgensen, W. L.; Chandrasekhar, J.; Madura, J. D.; Impey, R. W.; Klein, M. L. Comparison of Simple Potential Functions for Simulating Liquid Water. *J. Chem. Phys.* **1983**, *79*, 926−935.
(66) Tian, J.; Garcia, A. E. Simulation Studies of Protein Folding/Unfolding Equilibrium Under Polar and Nonpolar Confinement. *J. Am. Chem. Soc.* **2011**, *133*, 15157−15164.
(67) Miyamoto, S.; Kollman, P. A. SETTLE: An Analytical Version of the SHAKE and RATTLE Algorithm for Rigid Water Models. *J. Comput. Chem.* **1992**, *13*, 952−962.
(68) Hess, B. P-LINCS: A Parallel Linear Constraint Solver for Molecular Simulation. *J. Chem. Theory Comput.* **2008**, *4*, 116−122.
(69) Momany, F. A.; Appell, M.; Willett, J. L.; Bosma, W. B. B3LYP/6-311++G** Geometry-Optimization Study of Pentahydrates of α- and β-D-Glucopyranose. *Carbohydr. Res.* **2005**, *340*, 1638−1655.
(70) Arnott, S.; Scott, W. E. Accurate X-ray Diffraction Analysis of Fibrous Polysaccharides containing Pyranose Rings. Part I. The Linked-Atom Apporach. *J. Chem. Soc., Perkin Trans. 2* **1972**, *3*, 324−335.
(71) Brown, G. M.; Levy, H. A. α-D-Glucose: Precise Determination of Crystal and Molecular Structure by Neutron-Diffraction Analysis. *Science* **1965**, *147*, 1038−1039.
(72) Brown, G. M.; Levy, H. A. α-D-Glucose: Further Refinement Based on Neutron-Diffraction Data. *Acta Crystallogr., Sect. B: Struct. Sci.* **1979**, *B35*, 656−659.
(73) Chu, S. S. C.; Jeffrey, G. A. The Refinement of the Crystal Structures of β-D-Glucose and Cellobiose. *Acta Crystallogr., Sect. B: Struct. Sci.* **1968**, *24*, 830−838.
(74) Ferrier, W. G. The Crystal and Molecular Structure of β-D-Glucose. *Acta Crystallogr.* **1963**, *16*, 1023−1031.

(75) Hough, E.; Neidle, S.; Rogers, D.; Troughton, P. G. H. The Crystal Structure of α-D-Glucose Monohydrate. *Acta Crystallogr., Sect. B: Struct. Sci.* **1973**, *29*, 365−367.
(76) Kouwijzer, M. L. C. E.; van Eijck, B. P.; Kooijman, H.; Kroon, J. An Extension of the GROMOS Force Field for Carbohydrates, Resulting in Improvement of the Crystal Structure Determination of α-D-Galactose. *Acta Crystallogr., Sect. B: Struct. Sci.* **1995**, *51*, 209−220.
(77) Kirschner, K. N.; Woods, R. J. Solvent Interactions Determine Carbohydrate Conformation. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 10541−10545.
(78) Schnupf, U.; Willett, J. L.; Momany, F. DFTMD Studies of Glucose and Epimers: Anomeric Ratios, Rotamer Populations, and Hydration Energies. *Carbohydr. Res.* **2010**, *345*, 503−511.
(79) Hill, A. D.; Reilly, P. J. Puckering Coordinates of Monocyclic Rings by Triangular Decomposition. *J. Chem. Inf. Model.* **2007**, *47*, 1031−1035.
(80) Joint Commission on Biochemical Nomenclature. Conformational Nomenclature for Five and Six-Membered Ring Forms of Monosaccharides and Their Derivatives. *Eur. J. Biochem.* **1980**, *111*, 295−299.
(81) Bérces, A.; Whitfield, D. M.; Nukada, T. Quantitative Description of Six-Membered Ring Conformations Following the IUPAC Conformational Nomenclature. *Tetrahedron* **2001**, *57*, 477−491.
(82) Warren, G. L.; Patel, S. Electrostatic Properties of Aqueous Salt Solution Interfaces: A Comparison of Polarizable and Nonpolarizable Ion Models. *J. Phys. Chem. B* **2008**, *112*, 11679−11693.